1 Introduction and Literature Review

1.1 Hypertension

Hypertension (HTN) or high blood pressure is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular disease (EL-Guindy, 2005).

Hypertension is defined as persistent systolic blood pressure (BP) of at least 140 mm Hg and/or diastolic pressure of at least 90 mm Hg, or BP that is controlled to guideline-recommended levels using antihypertensive medication (Sobh, 2000; Rosendorf, 2005; Bishop *et al.*, 2010).

1.1.1 Epidemiology

Hypertension is an important public health challenge worldwide because of its high prevalence and concomitant increase in risk of disease. In 2005, approximately 75 million people had high BP: 34 million males and 39 million females. Data have established that death from ischemic heart disease and stroke increases progressively and linearly so that for every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP, there is a doubling of mortality from ischemic heart disease and stroke (Bishop *et al.*, 2010).

Hypertension was more prevalent in black women than in black men, 35.8 and 30.9% respectively, and in white women than in white men, 30.2 and 27.7%, respectively(Kearney *et al.*, 2004).earlier studies of hypertension prevalence in the Sudan were estimated at 7.5% (Elzubier *et al*,2000).

1.1.2 Classification of hypertension

The classification is based on the mean of two or more properly measured seated blood pressure readings on two or more office visits. Normal blood pressure is defined as levels <120/80 mmHg. Systolic blood pressure of 120-139 mmHg or diastolic blood pressure 80-89 mmHg is classified as prehypertension and those patients are at increased risk for progression to hypertension. Hypertension is divided into two stages. First stage includes patients with

systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg, second stage includes patients with systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg (El-Guindy, 2005).

Isolated systolic hypertension is defined as systolic blood pressure ≥140 mmHg and diastolic blood pressure <90 mmHg. Accelerated hypertension is characterized by markedly elevated blood pressure (diastolic blood pressure usually >120 mmHg) associated with retinal haemorrhage and exudates (grade 3), if untreated, it commonly progresses to malignant hypertension, which is characterized by papilloedema (grade 4) (El-Guindy, 2005).

1.1.2.1 Essential hypertension

Is systemic hypertension of unknown cause that results from dysregulation of normal homeostatic control mechanisms of blood pressure in the absence of detectable known secondary causes over 95% of all cases of hypertension are in this category In the mechanisms and theories of essential hypertension primary hypertension tends to cluster in families, but a specific genotype has not been identified. A number of associations have been suggested, but none has been confirmed (Rosendorf, 2005).

1.1.2.2 Secondary hypertension

Secondary hypertension is secondary to many diseases as renal diseases, endocrine diseases, neurological causes and pregnancy induced HTN and other diseases (Chiong *et al*, 2008). Secondary hypertension symptoms are according to the secondary disease as sleep apnea,Cushing's,hyperthyroidism, renal artery stenosis, polycystic kidney disease, adrenal tumors (Hui, 2011).

1.1.3 Complications and target organ damages of hypertension

Vascular Hypertrophy,left Ventricular Hypertrophy,heart Attack and Brain Attack, hypertensive Encephalopathy, hypertension Related Renal Damage, hypertensive Retinopathy, hypertensive emergencies and urgencies (Rosendorf, 2005).

1.1.4 Diagnosis of hypertension

1.1.4.1 Blood pressure measurement

Sitting pressures are usually adequate for routine measurement of blood pressure. Patients should sit quietly with back supported for 5 minutes, with arm bared and supported at the level of the heart in patients aged ≥65 years. Ambulatory blood pressure is usually several mmHg lower than office blood pressure (El-Guindy, 2005).

1.1.4.2 Laboratory investigations

Laboratory investigations should be directed at providing evidence of additional risk factors, searching for secondary hypertension and assessing presence or absence of target organ damage. They include routine tests, recommended tests and specific tests for extended evaluation of hypertensive complications and causes of secondary hypertension (El-Guindy, 2005).

1.1.5 Treatment of hypertension

Lifestyle modifications are often the only therapy indicated for patients with relatively mild hypertension and little overall cardiovascular risk, and they are always indicated along with drug therapy for the remainder.Drug therapy should begin if blood pressure remains above the goal of therapy after assiduous application of lifestyle modifications or if the patient starts with a blood pressure so high or cardiovascular risk (Rosendorf, 2005).

1.1.6 Prevention of hypertension

Prevention include, weight control, increased physical activity, limiting dietary sodium to ≤ 2.4 per day (equivalent to 6 g of sodium chloride), Abstention from alcohol and increased dietary potassium (El-Guindy, 2005).

1.2 Vitamin D

The generic term vitamin D designates a group of chemically related compounds that possess antirachitic activity. The two most prominent members of this group are vitamin D2 (Ergocalciferol) and vitamin D3 (Cholecalciferol), vitamin D does not meet the classical

definition of a vitamin. A more accurate description of vitamin D is that it is a prohormone and thus, vitamin D is metabolized to a biologically active form that functions as a steroid hormone (Zempleni *et al.*, 2007).

1.2.1 Vitamin D structure

Vitamin D refers to a family of structurally related compounds that display antirachitic activity. Member of the D- family are derived from cyclopentanoperhydrophenanthrene ring system, which is common to other steroids, such as cholesterol, vitamin D has only three intact rings; the B ring has undergone fission of the 9, 10-carbon bond resulting in the conjugated triene system that is present in all the vitamins (Zempleni *et al.*, 2007).

1.2.2 Vitamin D nomenclature

Vitamin D is named according to the new revised rules of the International Union of Pure and Applied Chemists (IUPAC). Vitamin D is designated seco because its B ring has undergone fission. Asymmetric centers are named using R, S notation and Cahn's rules of priority. The configuration of the double bonds is notated E, Z; E for Trans, Z for cis. The formal name for vitamin D3 is 9,10-seco(5Z,7E)-5,7,10(19)-cholestatriene- 3b-ol and for vitamin D2 it is 9,10-seco (5Z,7E)-5,7,10(19), 21-ergostatetraene-3b-ol (Zempleni *et al*, 2007).

1.2.3 Chemical properties

Vitamin D3 (C27H44O) Three double bonds; melting point, 848C 858C;Ultra violet(UV) absorption maximum at 264–265 nm with a molar extinction coefficient of 18,300 in alcohol or hexane, insoluble in H2O; soluble in benzene, chloroform, ethanol, and acetone; unstable in light; will undergo oxidation if exposed to air at 248C for 72 h; best stored at 08C. Vitamin D2 (C28H44O) Four double bonds; melting point, 1218C; UV absorption maximum at 265 nm with a molar extinction coefficient of 19,400 in alcohol or hexane, same solubility and stability properties as D3 (Zempleni *et al.*, 2007).

1.2.4 Isolation of vitamin D metabolites

Since vitamin D is a steroid, it is isolated from tissue by methods that extract total lipids, the technique most frequently used for this extraction is the method of Bligh and Dyer, over the years a wide variety of chromatographic techniques have been used to separate vitamin D and its metabolites. These include paper, thin-layer, column, and gas chromatographic methods (Zempleni ***et al*** , 2007).

1.2.5 Physiology of vitamin D

Vitamin D functions through its vitamin D endocrine system, vitamin D3 must be sequentially hydroxylated at the C-25 position and then the C-1 position to generate the steroid hormone, 1a, 25(OH) 2D3, before it can produce any biological effects. The activation of vitamin D2 occurs via the same metabolic pathway as that of vitamin D3, vitamin D2 has only 25%–30% of the biological activity of vitamin D3 (Zempleni ***et al.***, 2007).

1.2.6 Absorptionof vitamin D

Vitamin D can be obtained from the diet, in which case it is absorbed in the small intestine with the aid of bile salts, the specific mode of vitamin D absorption is via the lymphatic system and its associated chylomicrons,only about 50% of a dose of vitamin D is absorbed. However, considering that sufficient amounts of vitamin D can be produced daily by exposure to sunlight, it is not surprising that the body has not evolved a more efficient mechanism for vitamin D absorption from the diet (Zempleni ***et al***, 2007).

1.2.7 Synthesis of vitamin D

Chemical Synthesis of vitamin D is that vitamin D is derived from cholesterol, the first synthesis of vitamin D resulted from the first chemical synthesis of cholesterol, as a consequence of a hydrogen shift the top panel depicts the dynamic changes occurring within the seco-B conjugated triene framework of the hormone (C5, 6, 7, 8, 9, 10, 19). Photochemical Production of Vitamin D3 although the body can obtain vitamin D from the

diet, the major source of this prohormone can be its production in the skin from 7-dehydrocholesterol.The highest concentrations of 7-dehydrocholesterol are found in the stratum basale and the stratum spinosum (Smith *et al.*, 2004; Zempleni *et al.*, 2007; Nowson *et al.*, 2012).

1.2.8 Transport by vitamin D binding proteins (vitamin DBP)

Vitamin DBP, referred to group-specific component of serum or Gc-globulin, vitamin DBP is the serum protein that serves as the transporter and reservoir for the principal vitamin D metabolites throughout the vitamin D endocrine system, these include 25(OH) D3, the major circulating metabolite, and the steroid hormone 1α, 25(OH) 2D3. DBP binds 88% of the total serum 25(OH) D3 and 85% of serum 1, 25(OH) 2D3, yet only 5% of the total circulating DBP actually carries vitamin D metabolites, the concentration of the free hormone may be important in determining the biological activity of the 1α, 25 (OH) 2D3 steroid hormones (Zempleni *et al.*, 2007).

1.2.9 Storage of vitamin D

Following intestinal absorption, vitamin D is rapidly taken up by the liver thus blood has the highest concentration of vitamin D when compared with other tissues (Zempleni *et al.*, 2007).

1.2.10 Metabolism of vitamin D

Before vitamin D can exhibit any biological activity, it must first be metabolized to its active forms. 1α, 25(OH) 2D3 is the most active metabolite known, but there is evidence that 24, 25(OH) 2D3 is required for some of the biological responses attributed to vitamin D, vitamin D undergoes its initial transformation with the addition of a hydroxyl group to the 25-carbon to form 25(OH)D3, the major circulating form of vitamin D, the production of 25(OH) D3 is catalyzed by the cytochrome P450 enzyme, vitamin D3 25-hydroxylase, the kidney is considered the primary source of circulating 1α,25(OH)2D3. The major controls on the production of 1α, 25(OH) 2D3 are 1α, 25(OH) 2D3 itself, PTH, and the serum concentrations of calcium and phosphate (Bender *et al.*, 2003; Zempleni *et al.*, 2007).

1.2.11 Catabolism and excretionof vitamin D

The catabolic pathway for vitamin D is obscure, but it is known that the excretion of vitamin D and its metabolites occurs primarily in the feces with the aid of bile salts, very little appears in the urine (Zempleni *et al.*, 2007).

1.2.12 Physiological action of vitamin D

1.2.12.1 Action of vitamin D inendocrine system

The most clearly established effects of vitamin D are to maintain calcium and phosphate homeostasis, and to optimize bone health and muscle function. The hormonal form, 1, 25-(OH) 2D, increases active intestinal calcium (and phosphate) absorption, when calcium concentrations decrease below normal, even slightly, coupled to a G protein system, stimulate the secretion of parathyroid hormone. Parathyroid hormone then proceeds to the osteoblasts and to the proximal convoluted tubule cells within seconds. Most importantly, in the convoluted tubule cells that serve as the endocrine gland for the vitamin D hormone, 1-hydroxylase concentrations are markedly elevated. This signals the vitamin D hormone, which by itself stimulates intestinal absorption of calcium or together with parathyroid hormone, at higher concentrations, stimulates mobilization of bone calcium and renal reabsorption of calcium, the increase in serum calcium concentrations exceeds the set point of the calcium sensing system, shutting down the parathyroid gland-induced cascade of events (Norman, 2008; Katsilambros *et al.*, 2010; Harvey and Ferrier, 2011).

1.2.12.2 Non genomic action of vitamin D

The rapid or non-genomic responsesmediated by 1α, 25(OH) 2D3 were originally postulated to be mediated through the interaction of 1α, 25(OH) 2D3 with a novel protein receptor located on the external membrane of the cell, this membrane receptor has now been shown to be the classic VDR (heretofore largely found in the nucleus and cytosol) associated with caveolae present in the plasma membrane of a variety of cells (Zempleni *et al*, 2007).

1.2.12.3 Vitamin D in non-classical system

Nuclear receptors for 1α, 25(OH) 2D3 are found in a variety of tissues and cells not directly involved in calcium homeostasis, thus, the role of the vitamin D endocrine system has expanded to include a broader range of effects on cell regulation and differentiation, the expression of more than 100 proteins is known to be regulated by 1α,25(OH)2D3, including several oncogenes by far extending the classical limits of vitamin D actions on calcium homeostasis, the presence of muscle weakness or myopathy during metabolic bone diseases related to vitamin D deficiency (Zempleni *et al,* 2007).

1.2.12.4 Specific functions of active vitamin D

Active vitamin D (1α, 25 (OH) 2D3) and minerals metabolism, the classical target tissues for 1a,25(OH)2D3 are those that are directly involved in the regulation of mineral homeostasis, serum calcium and phosphorous, actions on Intestine**,** deficiency of vitamin D severely impairs intestinal transport of both calcium and phosphorus, although calcium uptake is usually accompanied by phosphate uptake, the two ions are transported by independent mechanisms, both of which are stimulated by 1, 25(OH) 2D3. Actions on bone**,** although the most obvious consequence of vitamin D deficiency is decreased mineralization of bone, 1,25(OH)2D3 apparently does not directly increase bone formation or calcium phosphate deposition in osteoid, actions on kidney**,** 1, 25(OH) 2D3 increases reabsorption of both calcium and phosphate.PTH secretion is increased in vitamin D deficiency, and hence tubular reabsorption of phosphate is restricted. actions on the parathyroid glands, the chief cells of the parathyroid glands are physiological targets for 1,25(OH)2D3 and respond to it in a manner that is characteristic of negative feedback Immunoregulatory Roles of 1α, 25(OH) 2D3**,**1α, 25(OH) 2D3 has been shown to affect cells of the immune system in a variety of ways.1α, 25(OH) 2D3 reduces the proliferation of HL-60 cells and also induces their differentiation to monocytes and macrophages. The actions of 1α, 25(OH) 2D3 on normal monocytes is controversial but it appears that it may enhance monocyte function. 1α, 25(OH) 2D3 appears to reduce levels of HLA-DR and CD4 class II antigens on monocytes or macrophages with no effect on the expression of class I antigens (Zempleni *et al.*, 2007; Harvey and Ferrier, 2011).

1.2.13 Nutritional requirements and recommended dietary allowance ofvitamin D

The vitamin D3 requirement of healthy adults has never been precisely defined. Since vitamin D3 is produced in the skin on exposure to sunlight and can be retained in vertebrate tissues, humans may not have a requirement for vitamin D when sufficient sunlight is available. The international unit (IU) of vitamin D3 is defined as ‘‘the vitamin D activity of 0.025 mg of the international standard preparation of crystalline vitamin D3. Thus, 1.0 IU of vitamin D3 is 0.025 mg (Zempleni *et al.*, 2007). the adequate intake allowance of vitamin D is 200 IU=day (5 mg=day) for infants, children, adult males, and females (including during pregnancy and lactation) up to age 51. For males and females ages 51–70 or more than 70, the adequate indicated level is set at 400 IU=day (10 mg=day) or 600 IU=day (15 mg=day), respectively (Goodman, 2002; Zempleni *et al.*, 2007).

1.2.14 Food sources of vitamin D

For the most part, vitamin D is present in unfortified foods in only very small and variable quantities. The vitamin D that occurs naturally in unfortified foods is generally derived from animal products. Salt-water fish such as herring, salmon, and sardines contain substantial amounts of vitamin D, and fish-liver oils are extremely rich sources. However, eggs, veal, beef, unfortified milk, and butter supply only small quantities of the vitamin. Plants are extremely poor sources of vitamin D; fruits and nuts contain no vitamin D; and vegetable oils contain only negligible amounts of the provitamin (Zempleni *et al.*, 2007).

1.2.15 Vitamin D deficiency

A deficiency of vitamin D results in inadequate intestinal absorption and renal reabsorption of calcium and phosphate, as a consequence, serum calcium and phosphate levels fall and serum alkaline phosphatase activity increases, in response to these low serum calcium levels, hyperparathyroidism occurs. Increased levels of PTH, along with whatever 1α, 25(OH) 2D3 is still present at the onset of the deficiency, result in the demineralization of bone, this ultimately leads to rickets in children and osteomalacia in adults (Zempleni *et al.*, 2007).

1.2.16 Hypervitaminosis D

Excessive amounts of vitamin D are not available from natural sources. However, vitamin D intoxication is a concern in those patients treated with vitamin D or vitamin D analogs for hypoparathyroidism, vitamin D-resistant rickets, renal osteodystrophy, osteoporosis, psoriasis, some cancers, or in those who are taking supplemental vitamins. Hypervitaminosis D is a serious problem as it can result in irreversible calcification of the heart, lungs, kidneys, and other soft tissues (Bender *et al.*, 2003; Zempleni *et al.*, 2007).

1.2.17 Vitamin D as hormone function

The steroid hormone 1α, 25-dihydroxyvitamin D_3 [1α, 25(OH) $_2D_3$] and its receptor, the vitamin D receptor (VDR), has resulted in significant contributions to good bone health in addition to the kidney's endocrine production of circulating 1α, 25(OH) $_2D_3$ a paracrine production of this steroid hormone in extrarenal organs. This article identifies the fundamentals of the vitamin D endocrine system, including its potential for contributions to good health (Deluca, 2004).

1.2.18 Biological mechanisms relating vitamin D with hypertension

1.2.18.1 Vitamin D and the Renin-Angiotensin System (RAS)

Dietary sodium and increased activity of the RAS are known to contribute to hypertension; salt restriction and inhibition of RAS activity reduce blood pressure. vitamin D as a proximal inhibitor of the RAS vitamin D may inhibit the RAS by reducing renin gene expression, increasing 1, 25$(OH)_2$D concentrations were associated with lower plasma renin activity in hypertension, both 25(OH)D and 1,25(OH)D were inversely associated with plasma renin and angiotensin II concentrations (Wang, 2009; Vaidya and Forman, 2010).

1.2.18.2 Vitamin D and intracellular calcium homeostasis

Calcium homeostasis has long been linked to blood pressure regulation; however, this concept evolved with the demonstrations that intracellular calcium concentrations were positively associated with blood pressure and that the flux of calcium into vascular smooth

muscle cells may be facilitated by 1,25$(OH)_2$D. This suggests that vitamin D may play a role in regulating vascular tone by influencing the concentration of calcium in vascular smooth muscle cells (Vaidya and Forman, 2010).

1.2.18.3 Vitamin D and other vascular mechanisms

In addition to potential effects on the RAS and regulation of vascular smooth muscle contractility, the link between vitamin D and hypertension has also been hypothesized to be mediated by other direct effects on vascular endothelium and smooth muscle.1, 25$(OH)_2$D as a vascular protective agent it reduces the deleterious effect of advanced glycation end products on the endothelium, reduces inflammatory and atherosclerotic parameters.1,25$(OH)_2$D has been implicated in the growth of vascular myocytes and has been shown to enhance prostacyclin production (possibly via the cyclooxygenase pathway) in cultured vascular smooth muscle cells (Vaidya and Forman, 2010).

1.2.18.4 Secondary hyperparathyroidism

There are also other mechanisms involved in the relationship between blood pressure and vitamin D. Secondary hyperparathyroidism, commonly seen in vitamin D deficiency, could be the reason for hypertension. The mechanism is not completely clear, but it is a well-known association that high PTH levels affect vascular smooth muscle cells and increase vascular stiffness and promotes hypertension (Jafari and Paknahad , 2012).

1.3 URIC ACID

Uric acid is the product of catabolism of the purine nucleic acids. Although it is filtered by the glomerulus and secreted by the distal tubules into the urine, most uric acid is reabsorbed in the proximal tubules and reused. Uric acid is relatively insoluble in plasma and at high concentrations, can be deposited in the joints and tissue, causing painful inflammation (Bishop *et al*,2010).

1.3.1Physiology

Uric acid, a weak organic acid with a pK_a of 5.75, is present principally as monosodium urate (MSU) at physiological pH values. Whereas in humans and the great apes, uric acid is the

end product of purine degradation, in other mammals, it is further degraded into allantoin by uricase, an enzyme that is mostly found in the liver. The gene encoding uricase underwent mutational silencing during hominid evolution .The consequence of uricase inactivation is the appearance of urate levels that are much higher in humans (≈240–360 μM) in comparison to other mammals (≈30–50 μM in mice). It has been proposed that higher serum levels of urate may be of selective advantage in the evolution of hominids because of its antioxidant effects. On the other hand, hyperuricemia is associated with multiple diseases in humans and points to the deleterious effects of high concentrations of urate.(Alexanderand,2010), purines such as adenosine and guanine from the breakdown of ingested nucleic acids or from tissue destruction,are converted into uric acid, primarily in the liver. Uric acid is transported in the plasma from the liver to the kidney, where it is filtered by the glomerulus (Bishop *et al* ,2010).

The kidney is the major site for removal of uric acid and accounts for two-thirds to three-fourths of the daily losses. Urate excretion is believed to depend on a system that includes four components: glomerular filtration, proximal tubular reabsorption, secretion, and postsecretory reabsorption. In primary hyperuricemia and gout, most patients demonstrate a defect in the renal handling of uric acid. In theory, failure of any of the model's components could be involved in the development of hyperuricemia in these patients. At present, the exact site of the defect remains unresolved.Diminished glomerular filtration rate and renal failure can lead to secondary hyperuricemia. Diuretics increase serum uric acid the remainder passes into the gastrointestinal tract and is degraded bybacterial enzymes. Nearly all of the uric acid in plasma is present as monosodium urate. At the pH of plasma (pH-7), urate is relatively insoluble; at concentrations greater than 6.8 mg/dL, the plasma is saturated. As a result, urate crystals may form and precipitate in the tissues(Bishop *et al* ,2010).

1.3.2 Clinical significance

1.3.2.1 Hyperuricemia

Hyperuricemia may be conveniently divided into two major categories. Symptomatic hyperuricemia is manifested by gout, nephrolithiasis, and uric acid nephropathy. A larger group of patients have asymptomatic hyperuricemia. Some of these patients will eventually become symptomatic.The risk of acute gouty arthritis increases with the level of serum uric acid and the duration of hyperuricemia. Acute fluctuations in serum uric acid may be

associated with the precipitation of acute gouty arthritis. Sudden reductions in serum uric acid may accompany the introduction of anti hyperuricemic therapy; hence, these patients often simultaneously begin prophylactic doses of colchicine (Walker *et al,* 1990).

Nephrolithiasis may accompany gouty arthropathy or occur as an independent problem. Uric acid forms radiolucent stones or may contribute to the formation of calcium stones. In patients with gout, the risk of stone formation rises with the level of serum uric acid. A better correlation exists between stone formation and urinary uric acid excretion. One study found the prevalence of stones to be 50% in gouty patients excreting greater than 1100 mg of uric acid per 24 hours.Acute uric acid nephropathy results from the precipitation of uric acid crystals within the collecting tubules and ureters. It is a severe form of acute renal failure and is classically associated with the chemotherapy of leukemias and lymphomas. It may also occur following strenuous exercise and epileptic seizures. Hyperuricosuria, aciduria, and urine concentration seem to act in concert to produce this syndrome(Walker *et al,* 1990).

The diagnosis can be made by the demonstration of a uric acid to creatinine ratio greater than 1 in the setting of acute renal failure.Routine screening of hospitalized patients will identify a substantial number with elevated serum uric acid and no related symptoms. Most of these patients will remain asymptomatic throughout their lives. A complete discussion of the management of asymptomatic hyperuricemia is beyond the scope of this chapter. Suffice it to say that the weight of current evidence speaks against the normalization of uric acid in asymptomatic patients. Regardless of the level of uric acid, little seems to be lost by awaiting the onset of the first bout of arthritis or kidney stone. (Walker *et al,* 1990)

1.3.2.2 Hypouricemia

Hypouricemia is commonly defined as a serum urate concentration of 2 mg/dl or less. A low serum urate concentration may result from decreased production or increased excretion. Quantification of urinary uric acid can facilitate a distinction between these two mechanisms. Patients with hypouricemia secondary to impaired production will have little or no urinary uric acid.Hypouricemia can be found in about 1% of hospitalized patients. In most cases the cause is related to drugs, including salicylates, allopurinol, x-ray contrast agents, and glycerylguaiacholate. Forced diuresis, used mainly in the treatment of suicide-attempt patients and renal colic, may result in hypouricemia. Total parenteral nutrition can cause profound hypouricemia in some patients(Walker *et al,*1990).

Several malignant diseases have been associated with hypouricemia, including Hodgkin's disease, sarcoma, glioblastoma, and a variety of carcinomas. In multiple myeloma, light chains most likely cause tubular epithelial damage and Fanconi syndrome. Other malignancies have also been associated with tubular dysfunction and increased renal clearance of urate. The inappropriate secretion of antidiuretic hormone that accompanies some malignancies may lower serum uric acid. Decreased xanthine oxidase activity, acquired after the development of a malignancy, appears to be an uncommon mechanism.

Hypouricemia produces no symptoms or known morbidity. Its fortuitous discovery on automated chemistry screening requires no therapy but should alert the physician to search for an underlying cause (Walker *et al*,1990).

1.3.4Relationship between hypertension and uric acid

Epidemiologic studies published during the past 3 years support the possible role of uric acid in the onset of essential hypertension. Data from several large, longitudinal cardiovascular disease studies indicate that elevated serum uric acid is a predictor of incident hypertension and blood pressure progression (DanieI *et al*,2006).

hyperuricemia results in renal vascular inflammation (through stimulation of nuclear transcription factors and release of proinflammatory cytokines) a preglomerulararteriolopathy (attributable to increased vascular smooth cell proliferation via increased expression of mitogen-activated protein kinases, cyclooxygenase-2,and platelet-derived growth factor), and tubulointerstitial inflammation and fibrosis. These renal changes result in activation of the renin-angiotensin system. Increased intrarenal vasoconstriction ensues with a reduction in single nephron glomerular filtration, decreased sodium filtration, and a rightward shift in the pressure–natriuresis relationship. Eventually, a salt-sensitive form of hypertension sets in. Indeed, it has been hypothesized that uricase gene mutation in humans in the Miocene era led to relative hyperuricemia and an increased BP response to sodium. Additional contributory mechanisms include increased juxtaglomerular renin production and reduced neuronal NO synthase in the macula densa A possible role for insulin resistance as a common precursor of hyperuricemia and hypertension has also been proposed. Additionally, it is possible that UA is an indicator of subtle renal dysfunction that, in turn, promotes hypertension (Sundstrom *et al*, 2004).

Hyperuricemia is associated with hypertension, vascular disease, renal disease, and cardiovascular events. In the epidemiologic evidence and potential mechanisms for this association, experimental studies that demonstrate that uric acid is not inert but may have both beneficial functions (acting as an antioxidant) as well as detrimental actions (to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction). A recently developed experimental model of mild hyperuricemia also provides the first provocative evidence that uric acid may have a pathogenic role in the development of hypertension, vascular disease, and renal disease. Thus, it is time to reevaluate the role of uric acid as a risk factor for cardiovascular disease and hypertension and to design human studies to address this controversy (Johnson, 2006).

1.4 Rationale

In Sudan hypertension disease is in increase in both sex's males and females and occurs in different age groups, it can cause many organ damages and dysfunctions. Hypertension is a major risk factor for stroke, ischemic heart disease, peripheral vascular disease, heart failure and chronic kidney disease. Vitamin D is one of the factors that can affect blood pressure. Nowadays, vitamin D has been considered, due to its various effects on health, and numerous studies have been conducted on its various effects on different parts of body and proper functioning of different organs and systems. It is also claimed that vitamin D deficiency leads to many chronic diseases and insufficient intake of vitamin D plays an important role in pathogenesis and progression of hypertension.

Uric acid is not inert but may have both beneficial functions (acting as an antioxidant) as well as detrimental actions (to stimulate vascular smooth muscle cell proliferation and induce endothelial dysfunction), elevated serum uric acid is a predictor of incident hypertension and blood pressure progression. Uric acid causes hypertension through the activation of the rennin angiotensin system, downregulation of nitric oxide, and induction of endothelial dysfunction and vascular smooth muscle proliferation.

1.5 General objective

To evaluate uric acid levels among hypertensive vitamin D deficient patients in Khartoum State.

1.6 Specific objectives

1- To estimate vitamin D levels in study group.

2- To estimate uric acid levels in study group.

3- To Correlate between vitamin D levels and study variables (age, BMI, gender and duration).

4- To Correlate between uric acid level and study variables (age, body mass index, gender and duration).

2 Materials and Methods

2.1 Materials

2.1.1 Study Design

Descriptive cross-sectional study, to estimate serum Vitamin D and Uric acid levels in Sudanese Hypertensive patients conducted during the period of March to July 2014.

2.1.2 Study Area

This study was carried out in different hospitals, clinic and centers (East nile model hospital, Khartoum teaching hospital, Alfaroug medical center) in Khartoum state

2.1.3 Study Population

The targeting group in this study is eighty eight hypertensive patients.

2.1.4 Inclusion criteria

Specimens were collected from hypertensive patients, serum specimens collected from these patients when they were fasting.

2.1.5 Exclusion criteria

Other diseases like diabetes mellitus, renal diseases and patients under vitamin D supplement are excluded.

2.1.6 Collection of samples

samples were collected by using dry, plastic syringes, tourniquet was used to make the veins more prominent, blood samples (5ml) was collected in plane containers from each volunteer under septic condition. All blood samples were allowed to clot at room temperature, then they were centrifuged at 4000 rpm to obtain the serum samples, and stored in -20° until the analysis.

2.1.7 Ethical Considerations

Study was approved from ethical committee of the Sudan University of Science and Technology, verbal informed consent was obtained and all patients were informed by aim of the study

2.2 Methods

2.2.1 Vitamin D Estimation

2.2.1.1 Principle

The ELISA kit is designed for the in vitro determination of 25-OH Vitamin D in human serum or plasma samples. In the first analysis step, the calibrators and patient samples are

diluted with biotin labeled 25-OH Vitamin D and added to micro plate wells coated with monoclonal anti-25-OH Vitamin D antibodies. During the incubation an unknown amount of 25-OH Vitamin D and known amount of biotin labeled 25-OH Vitamin D compete for the antibody binding sites in micro plate wells plate. Unbound 25-OH Vitamin D is removed by washing. For the detection of bound biotin labeled 25-OH Vitamin D, a second incubation is performed using peroxidase labeled streptavidin. N a third incubation using the peroxidase substrate tetramethylebenzidene (TMB) the bound peroxidase promote the color reaction. The color intensity is inversely proportional to the 25-OH Vitamin D concentration in the sample. Results of the samples calculated directly using a standard curve.

2.2.1.2 Procedure

Prior to use in the assay, reagents and samples were stand at room temperature, samples (200µl) were pipette in biotin/sample buffer for dilution, in each micro plate wells, and then plate incubated for 2 hours at room temperature, the wells were emptied and subsequently washed three times using 300 µl of working strength wash buffer for each wash, enzyme conjugate streptavidin/peroxidase (100µl) were pipette into each of the micro plate wells and Incubated for 30 minutes at room temperature, wells were emptied and washed as step 3. Chromogen substrate solution (100µl) was pipette into each of the micro plate wells and Incubated for 15 minutes at room temperature. Stop solution (100µl) was pipette into each of the micro plate wells in the same speed and the same order as chromogen substrate solution was introduced. Photometric measurement of the color intensity was made at a wavelength 450 nm and a reference wavelength 620 nm and 650 within 30 minutes of adding stop solution. Prior to measuring the micro plate was shacked slightly to ensure homogenous distribution of the solution.

2.2.1.3 Calculation of Results

The standard curve from which the 25-OH vitamin D in the serum samples can be taken was obtained by point-to-point plotting of the extinction values measured for six calibration sera against the corresponding units. Use “4-PL” or “cubic-spline” plotting for calculation of the standard curve by computer.

2.2.1.4 Detection Limit

The lower detection limit is defined as the mean value of an analyte-free sample minus three times the standard deviation and is the smallest detectable 25-OH vitamin D concentration. The detection limit of 25-OH vitamin D ELISA is 1.6 ng/ml.

2.2.1.5 Linearity

The linearity of the test was investigated by diluting three samples with calibrator one and determining the concordance. The average concordance amounted to 98%.

2.2.2 Uricase /peroxidase for uric acid estimation:

2.2.2.1 Principle

Uric acid in the sample originates,by means of the coupled reaction described below

Uric acid $+O_2 +2\ H_2O$ $\xrightarrow{\text{uricase}}$ allanation$+CO_2+H_2O_2$

$2\ H_2O_2 +$4-aminoantipyrine + DCFS $\xrightarrow{\text{Peroxidase}}$ Quinoneimine + $4H_2O$.

2.2.2.2 Reagents:

Phosphate,detergent, dichlorophenolsulfonate, uricase, ascorbate oxidase, 4-aminoantipyrine.

Uric acid Standard:6 mg/dl

2.2.2.3.Procedure:

Reagents were brought at room temperature, briefly according to manufactured 10 ul of standard, samples were added to 1000 ul working reagent. Then mixed thoroughly and incubated for 5 min at room temperature, absorbance measured against blank at 520 nm, then concentration calculated according to following formula using Biosystem BTS-310 spectrophotometer.

Serum and plasma: (A) sample/ (A) standard × 6 (standard Conc.) in mg/dl.

2.2.3 Statistical analysis

The data was analyzed using statistical package of social science (SPSS computer program 16), all result expressed as precentage and (Mean±SD) and significant differences considerd as *p*-value <0.05, using frequency, independant t-test and persons correlation regresion.

3 Results

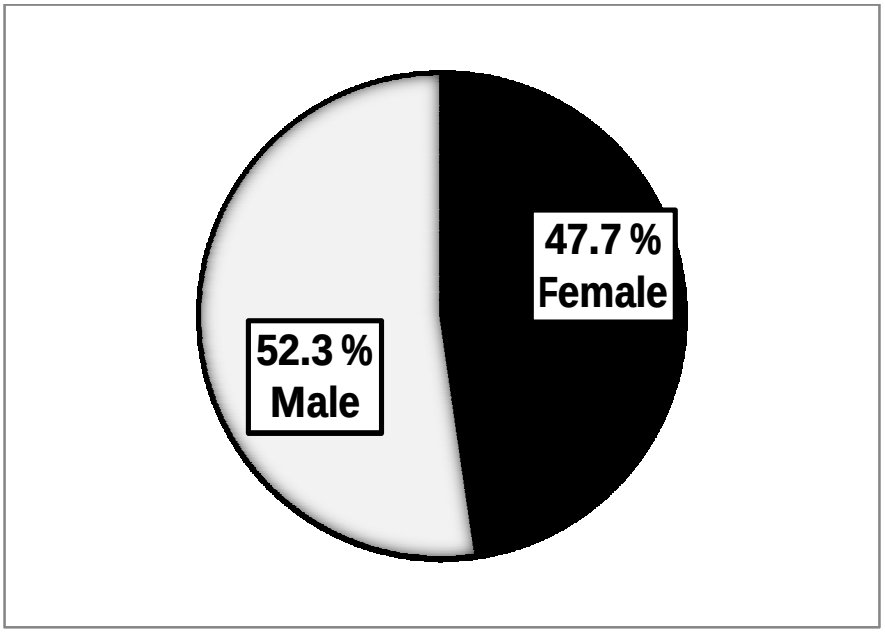


Fig.3.1 Shows frequencies of gender among hypertension patients, results expressed as percentage (%).

Table.3.1 Shows frequencies of BMI normal weight BMI <26.5 kg/m^2 and over weight BMI >25 kg/m^2 in study group classified as male and female, result expressed as percentage (%).

BMI	**Gender**	
	Male	Female
Normal weight	19.6%	33.3%
Over weight	80.4%	66.7%
Total (%)	100%	100%

Table.3.2 Shows frequencies of gender (male and female) in study subgroups classified according to vitamin D level, result expressed as percentage (%).

Vitamin D groups	**Gender**	
	Male	Female
Normal vitamin D	54.4%	19.00%
Deficient vitamin D	37.0%	31.00%
Sever deficient vitamin D	8.60%	50.00%
Total(%)	100%	100%

Table.3.3 Shows frequencies of vitamin D level in study group classified as gender that have normal weight and other who have over weight, result expressed as percentage (%).

Vitamin D groups	**BMI**			
	Normal weight		Over weight	
	Gender			
	Male	Female	Male	Female
Normal vitamin D	25.3%	35.7%	50.0%	10.7%
Deficient vitamin D	74.7%	43.0%	39.5%	25.0%
Sever deficient vitamin D	00.0%	21.3%	10.5%	64.3%
Total(%)	100%	100%	100%	100%

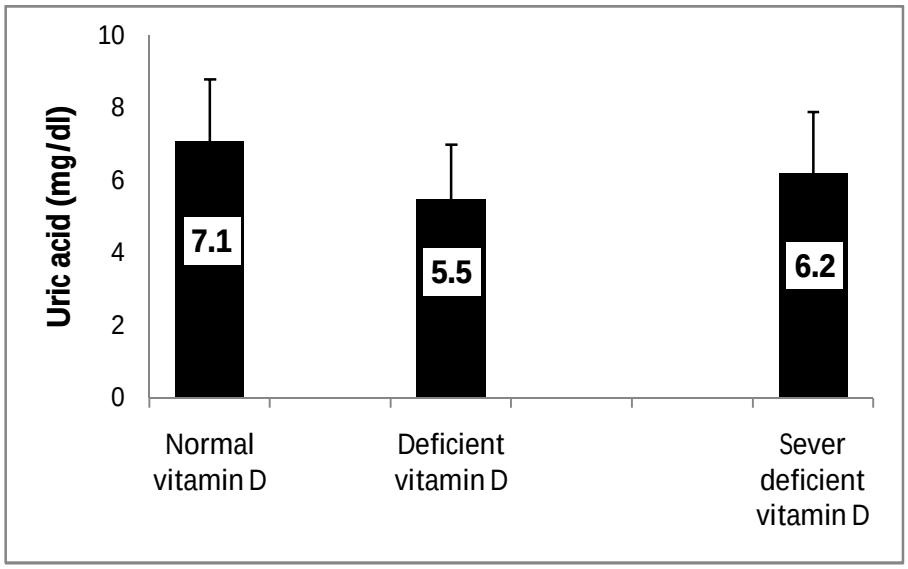


Fig (3.2) Showed mean of uric acid level in study subgroups classified according to vitamin D level, result expressed as (M ± STD). Vitamin D patients result in (*P*-value 0.001) and sever deficient (p-value 0.000) compared with control group.

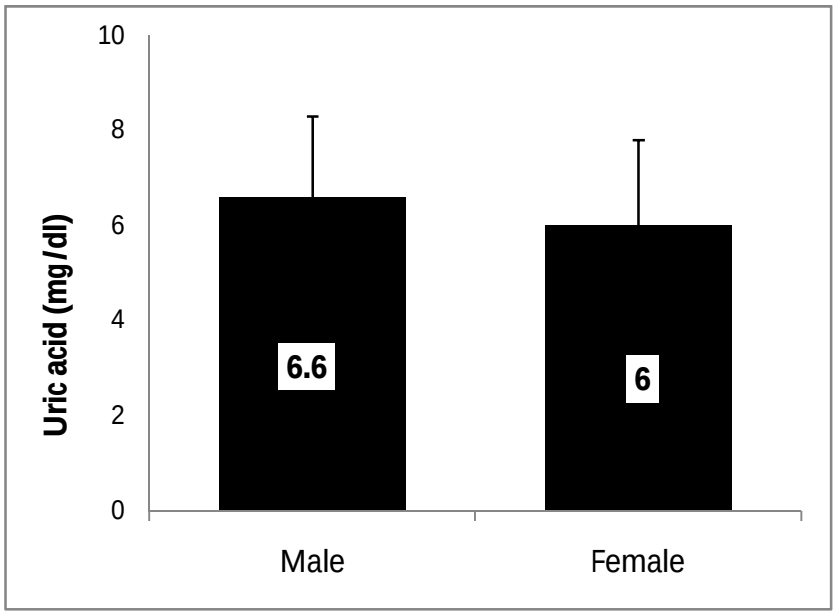


Fig (3.3) Showed mean of uric acid level in study group classified as male and female, result expressed as (M ± STD),(*P*-value 0.119).

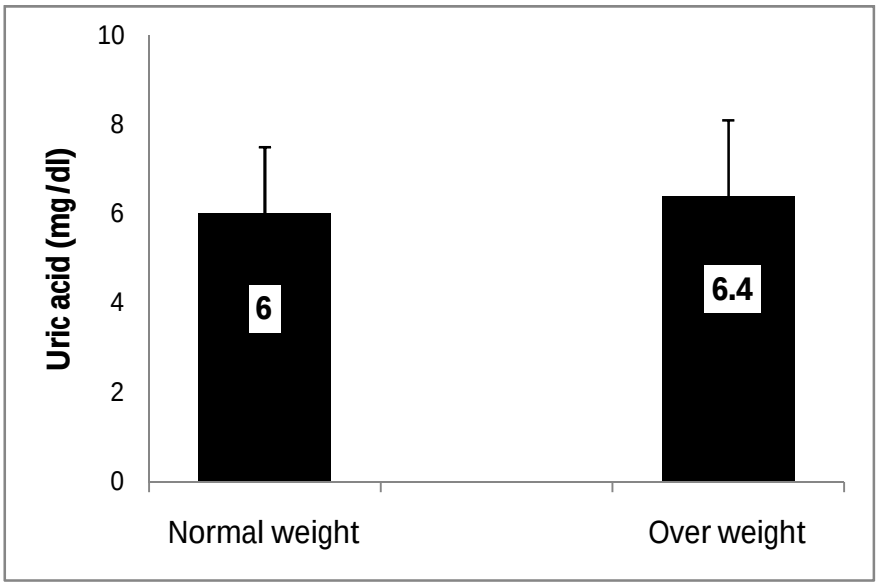


Fig (3.4) Showed mean of uric acid level in study group classified as normal weight (BMI ≤ 25 kg/m^2)and over weight (BMI > 25 kg/m^2), result expressed as (M ± STD), (*P*-value 0.343)

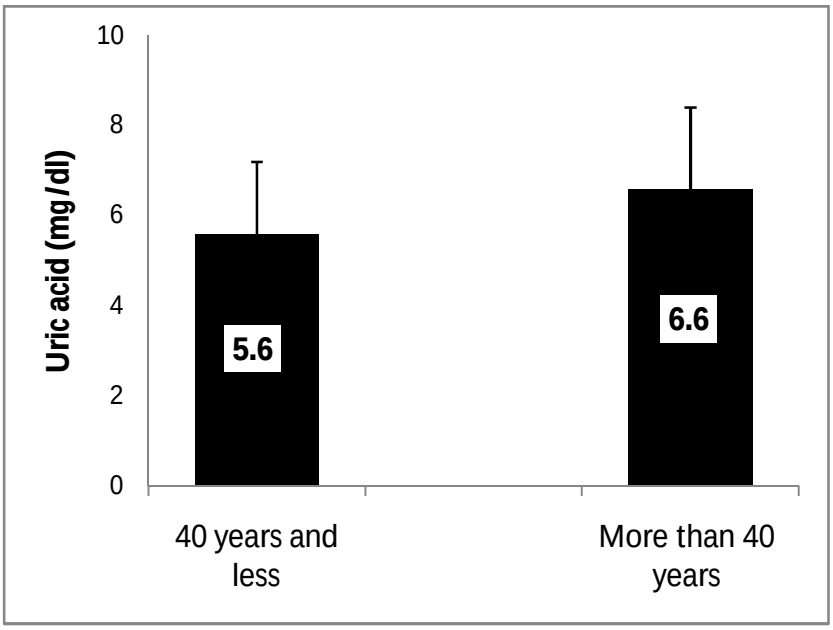


Fig (3.5) Showed mean of uric acid level in study group classified as 40 years and less and more than 40 years, result expressed as (M ± STD), (*P*-value 0.018)

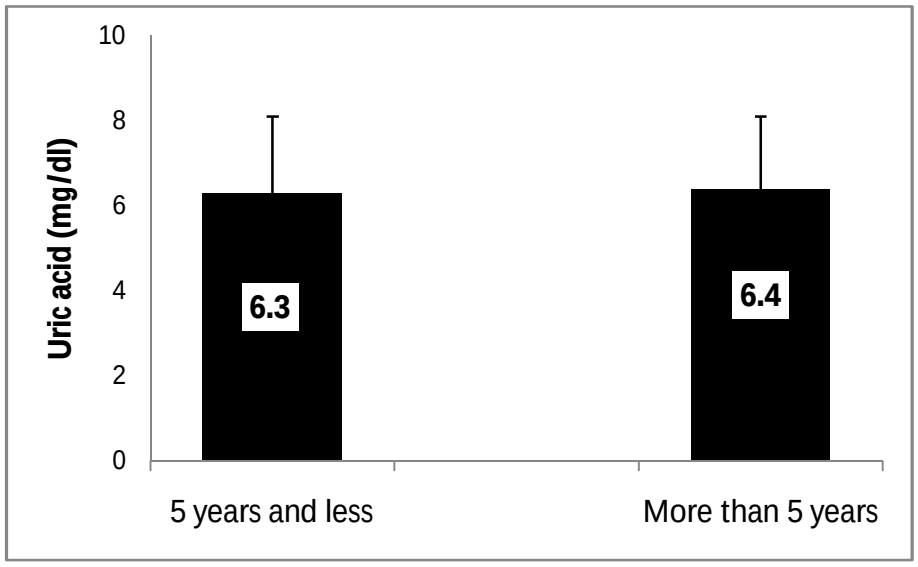


Fig (3.6) Showed mean of uric acid level in study group classified as group with disease for 5 years and less and other with disease for more than 5 years, result expressed as (M ± STD), (*P*-value 0.805).

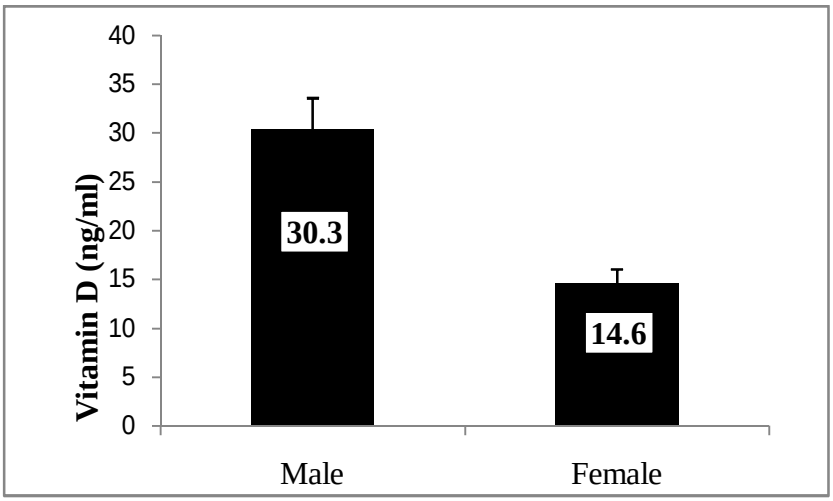


Fig.(3.7) Shows mean of vitamin D level in study group classified as male and female, result expressed as (M ± STD) with (*P*-value 0.000).

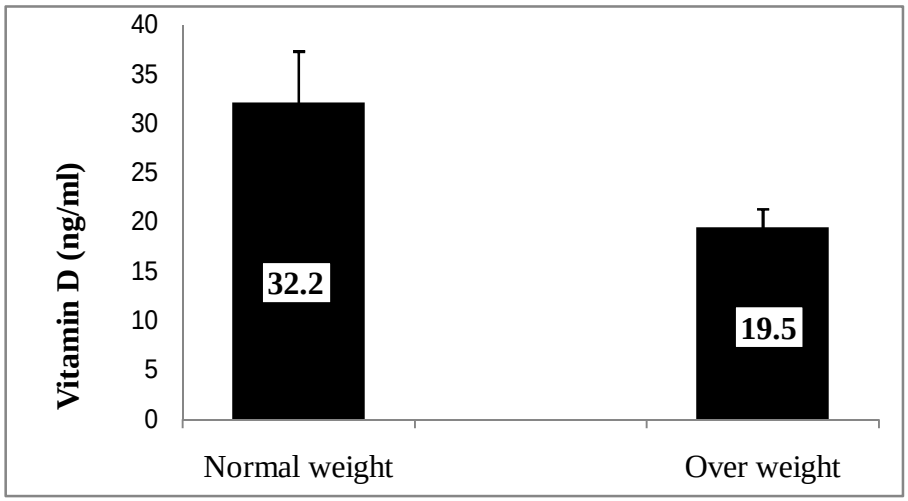
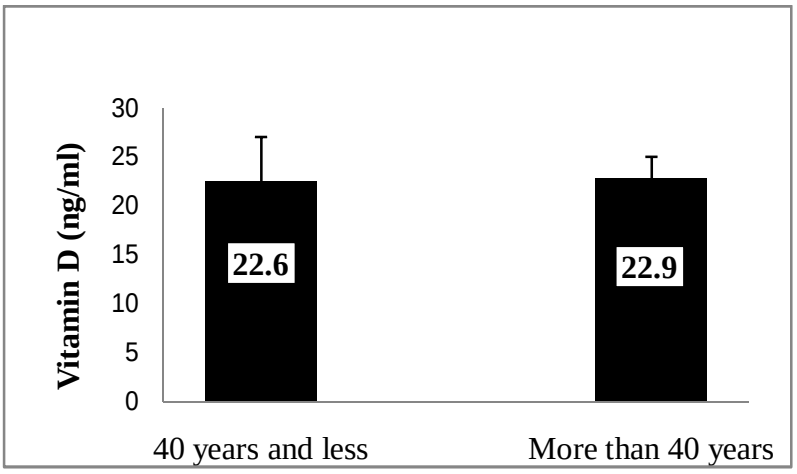


Fig.(3.8) Shows mean of Vitamin D level in study group classified as normal weight (BMI ≤ 25 kg/m^2)and over weight (BMI > 25 kg/m^2), result expressed as (M ± STD), with (*P*-value 0.033).



Fig(3.9)Shows mean of Vitamin D level in study group classified as 40 years and less and more than 40 years, result expressed as (M ± STD),with (*P*-value 0.959).

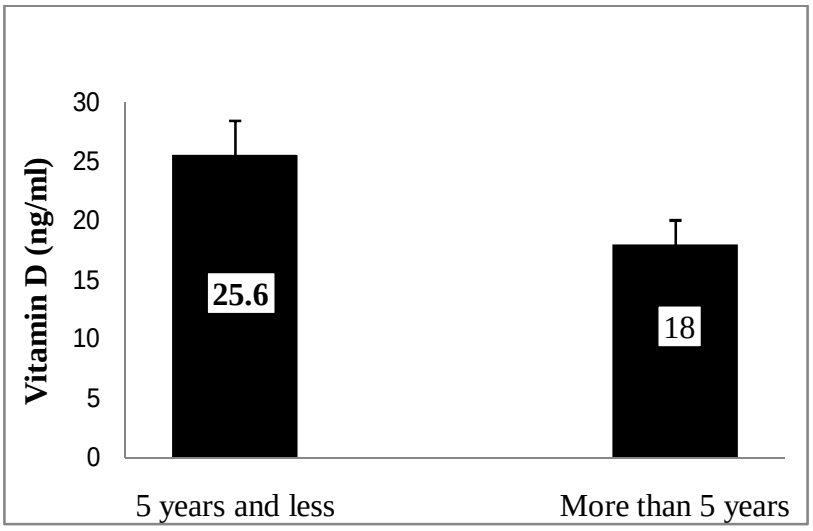


Fig.(3.10) Shows mean of Vitamin D level in study group classified as group with disease for 5 years and less and other with disease for more than 5 years, result expressed as (M ± STD), with (*P*-value 0.041).

Table (3.4) Pearson correlation analysis shows the correlation between vitamin D and uric acid, result expressed as (Pearson's r: 0.288, P: 0.033).

		Vitamin D
Uric acid	Pearson Correlation (r)	+0.288
	Sig	0.033
	N	88

r = Correlation coefficient = +0.288 (positive correlation)

+ = Positive correlation

Sig= Strength of correlation= 0.033 (weak correlation)

N = Number of patient

4. Discussions

Hypertension is a major health problem throughout the world because of its high prevalence and its association with increased risk of cardiovascular disease **(EL-Guindy, 2005)**, in addition to potential effects on the RAS and regulation of vascular smooth muscle contractility, vitamin D has direct effects on vascular endothelium and smooth muscle**(Vaidya and Forman, 2010),**uric acid is mono-anion urate, traditionally considered to be a metabolically inert end-product of purine metabolism in man, without any physiology value. However, this ubiquitous compound has proven to be selective antioxidant**(Ames , 1993),** uric acid is also associated with cardiovascular disease and the metabolic syndrome, and also the onset of hypertension **(Schachter, Michael, 2005).**

Therefore this descriptive cross-sectional study was done to evaluate uric acid levels among vitamin D deficient hypertensive patients in Khartoum State during the period of March to July 2014, in addition to correlate between vitamin D, uric acid level and study variables (age, BMI, gender and duration), in order to achieve the objective of the study eighty eight hypertensive patients, classified based on vitamin D level as normal, deficient, sever deficient vitamin D patients.

The results of frequencies showed that the percentage of hypertensive males (52.3%) is approximately equal to females (47.7%), this observation agreed with previous reportthat blood pressure is higher in men than in women at similar ages,another study has been designed to assess the prevalence of hypertension in Lebanese population they found, no statistically significant difference between male and female patients **(Tohme *et al*, 2005; Reckelhoff, 2014)**.

In addition our study observed hypertensive male were more overweight (80.4%) than female (66.7%), these finding indicate that hypertensive male are more susceptible to gaining weight than female, and thus complication of hypertension, obesity and weight gain have been identified as the most important determinants of hypertension, by which 10% rise in body weight explains a 7 mm Hg rise in systolic blood pressure **(Diaz, 2002)**. Also the current study observed that, vitamin D deficient is more common in female (81.0%) than male whom account (45.0 %), our justification the Sudan male are more exposed to the sun light than female which may enhance the synthesis of vitamin D by breaking B-carbon ring of cholesterol **(Binkley *et al*., 2007)**.

The results of current study revealed, vitamin D levels was not affected BMI in the males while in females with higher BMI tend to have vitamin D deficiency, this indicate that obesity is associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D from cutaneous and dietary sources because of its deposition in body fat compartments, serum vitamin D was also negatively correlated with BMI and body fat mass, different mechanisms relating hypovitaminosis D to obesity occur concurrently thus vitamin D is affected by BMI, vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity **(Worstman *et al* , 2000; Parikh *et al,* 2004; Snijder *et al*., 2005; McGill *et al*., 2008).**

The results provide exponential evidence that mean uric acid concentration significantly decrease in vitamin D deficient followed by sever deficient groups in comparison with control group with (*p*-value 0.001 and 0.026) respectively, this finding indicate the role of uric acid as antioxidant which may increase the formation of free radical in both vitamin D deficient and sever deficient group, lead to early complication of hypertension specially in hypertensive patients with vitamin D deficient. Uric acid may function as an antioxidant, and possibly one of the most important antioxidants in plasma and acute elevations in uric acid may provide some anti-oxidant protection**(Sautin, 2010)**.

Women tend to have lower levels of uric acid than men, probably because of the uricosuric effect of estrogens **(Daniel *et al,* 2008)**, and also with other they reported thatserum uric acid was significantly higher in men than in women. **(Matsumura *et al,* 2006).**The present study noted that insignificant difference in mean uric acid concentration of female compared with male with (*p*-value 0.119). in addition mean uric acid level inoverweight showed insignificant difference when compared with normal weight group with (*p*-value 0.343) in contrast with previous study report, the uric acid was positively associated with BMI that serum uric acid may be involved in the obesity, which in turn may explain the relation of serum uric acid to coronary atherosclerosis And hypertension **(Lee *et al,*1995)**, other linking hyperuricaemia with CVD risk **(Kuzuya *et al,*2002; Bonora *et al,*1996)**

The present study revealed that, there is significant increase in the mean of uric acid with age groups with (*P*-value0.018) these findings confirm with previous study they found that serum uric acid levels in men and women increased with advancing age **(Kuzuya *et al,* 2002)**.

The results of current study revealed insignificant difference of mean uric acid concentration with duration of hypertension groups *P*-value (0.805) in contrast with previous studies reported serum uric acid level independently predicted the development of hypertension (**Perlstein *et al,* 2006; Sundstrom *et al,* 2004)**.

Females were more susceptible to vitamin D deficiency more than males our present study revealed that, there is significant decrease in the mean of vitamin D level in female when compared with male (*P*-value 0.000),Sudanese males expose to sun more than females according to the some hard nature of work in Sudan, and exposure to sun light is main source for vitamin D synthesis, the maximalvitamin D concentration produced by natural UV exposure **(Binkley *et al,* 2007)**.also overweight group noted that have less vitamin D level when compared withnormal weight groupwith *P*-value (0.033),this finding confirm with previous studies there found that there is an inverse association between BMI and the serum levels of vitamin D,vitamin D status is strongly associated with variation in subcutaneous and especially visceral adiposity **(Konradsen *et al,* 2008; Cheng *et al,* 2010; Lagunova *et al,* 2009)**.

Vitamin D level was not affected by the age ,the present study revealed that insignificant difference when compared age groups with the mean of vitamin D levelswith *P*- value (0.959), these results confirmedby previous study reported that no effect of age on the vitamin D concentration **(Sherman *et al,* 1990)** also there is significant decrease in the mean of vitamin D level of long duration of disease with (*P*-value 0.041), these findings confirm the role of vitamin D in the hypertension, in more than 20 previous cross-sectional studies have examined the association between plasma vitamin D and either blood pressure or prevalent hypertension. The great majority of these studies demonstrate that lower circulating levels vitamin Dwere associated with higher blood pressures or a higher prevalence of hypertension **(Vaidya and Forman, 2010)**.

Finally, this present study showed week positive correlation between vitamin D and uric acid (*P*-value0.033), (Pearson's r: +0.288), this results is confirm the role of uric acid as antioxidant. Uric acid is a powerful scavenger of singlet oxygen, peroxyl radicals ($RO^{\cdot}_2$) and hydroxyl radicals ($^{\cdot}OH$). Urate circulating in elevated concentrations was proposed to be one of the major antioxidants of the plasma that protects cells from oxidative damage**(Sautin, 2010).**

Conclusion

The study conclude that, percentage of vitamin D deficient females is slightly more than males, there is significant increase vitamin D level of male compared with female, study observed frequency of overweight are common in both hypertensive gender groups but hypertensive male tend to gaining weight more than female.

Uric acid showed significant decrease in both cases (deficient and sever deficient) compared with control group, which may both vitamin D deficient and decease in uric acid lead to increased tissue damage and thus develop of early complication in hypertensive patients with vitamin D deficient.

Recommendations

More research should be performed with other parameters(vitamin D receptor, lipid profile ,protein level) to clarify underline mechanisms behind the metabolism of uric acid and vitamin D in hypertensive patients .

Monitoring of uric acid and vitamin D is recommended for hypertensive patients, so as to design vitamin D supplementation protocol to prevent the tissue damage, especially in female because they at risk of vitamin D deficient.

Reduce body weight in hypertensive subject is recommended in order to prevent develop of early complication in hypertensive patients.

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